whose sequence is that of SEQ ID NO:2 or 4, which polypeptide is capable of binding to one or more of MORT-1 and MACH.

REMARKS

Claims 44-61 and 63-68 presently appear in this case. No claims have been allowed. The official action of November 9, 2001, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to polypeptides that are capable of binding to one or more of MORT-1 and MACH and which have the amino acid sequence of a G1 protein isoform whose sequence is that of SEQ ID NO:2 or 4. The invention also relates to fragments, analogs and derivatives of such polypeptide, as well as DNA sequences which encode such polypeptide. Vectors comprising such DNA sequences, host cells containing such vectors and methods of producing the polypeptide by growing such host cells are also part of the present invention, as are pharmaceutical compositions and methods for the modulation of cell death or inflammatory processes by introducing such polypeptide into cells.

The examiner has objected to the Information Disclosure Statements of February 29, 2000, and September 17, 2000, with respect to the listings of journal article AI and foreign patent AP. The examiner has given applicants an opportunity to file a new 1449 properly citing these two documents with the response to this Office Action. A copy of such a new form 1449 is attached hereto.

It is noted that the examiner has reconsidered and withdrawn the restriction requirement except for claims 60-62. The examiner states new claims 60 and 62 encompass DNA therapy and protein therapy that were in separate groups in restriction paper no. 11. The examiner considers claims drawn to protein therapy to be considered non-elected because they are directed to a second method of using the claimed product. The examiner has withdrawn claims 60-62 insofar as they encompass polypeptide therapy from further consideration as being drawn to a non-elected invention. The examiner states that claims 44-62 insofar as they include DNA therapy and insofar as they encompass SEQ ID NOs:1, 2, 3 and 4 are considered to be elected and pending examination. This restriction requirement is respectfully traversed.

Applicants do not traverse the examiner's consideration that only a first method of use need be examined; however, applicants traverse the examiner's consideration that it is the DNA therapy that was constructively elected and the protein therapy non-elected. Claim 16, as originally presented, was drawn to the method of use, and the first method disclosed in that claim was a method of protein therapy, and the second method disclosed therein was a method of DNA therapy. Thus, the first-listed claimed process is a process of protein therapy. The fact that the method of use was mentioned in Group I of the restriction requirement is irrelevant as the examiner has agreed with applicants that Groups I and II should have been combined. If they had been combined in the first place, then the first-

presented method of use for the DNA/peptide product would have been the method of protein therapy.

Claim 60 has now been amended in order to delete reference to DNA therapy, as has claim 61, and claim 62 has now been deleted without prejudice toward the filing of a divisional application. It is respectfully requested that the examiner consider that protein therapy is the elected method of use and that all of the claims now present in the case be further examined.

Claims 44-62 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The examiner agrees that the specification is enabling for a DNA sequence comprising either SEQ ID NO:1 or 3 or encoding amino acid sequence of SEQ ID NO:2 or 4, which sequences are capable of binding to MORT-1 and/or MACH proteins, a vector comprising such DNA, a host cell containing such a vector, a method for producing a polypeptide of SEQ ID NO:2 or 4, and a polypeptide of SEQ ID NO:2 or 4 which is capable of binding to MORT-1 and/or MACH protein. However, the examiner states that the specification does not reasonably provide enablement for the rest of the disclosed embodiments. More specifically, the examiner does not consider fragments of the polypeptide to be enabled or analogs that differ by no more than ten substitutions, deletions and/or insertions or functional derivatives. Further the examiner does not consider proteins capable of binding to Mch4 to be enabled. This rejection is respectfully traversed.

First of all, new claims 63-68 have now been added drawn only to the embodiments that the examiner concedes to be

enabled. Thus, regardless of whether or not the examiner reconsiders this rejection with respect to the remaining claims, it is requested that the examiner explicitly indicate that claims 63-68 are not subject to any enablement rejection.

With respect to the examiner's statement that the specification is not enabled for either a polypeptide or DNA sequence which encodes such a polypeptide which is capable of binding to Mch4, the claims have now been amended in order to delete reference to Mch4, thus obviating this part of the rejection.

The enablement requirement of 35 U.S.C. §112 is discussed at section 2164 *et seq* of the MPEP. MPEP §2164.01 states that any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The question is whether the experimentation needed to practice the invention is undue or unreasonable. If the invention can be practiced without undue or unreasonable experimentation, the enablement requirement is considered to be met. The undue experimentation factors of In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) are set forth at MPEP §2164.01(a). These factors include:

(a) the breadth of the claims;

(b) the nature of the invention;

(c) the state of the prior art;

(d) the level of one of ordinary skill;

(e) the level of predictability in the art;

(f) the amount of direction provided by the inventor;

(g) the existence of working examples; and

(h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the examiner takes the position that the scope of the claims is broader than the enabled disclosure with respect to fragments of the disclosed polypeptide sequences, with respect to analogs thereof, and with respect to functional derivatives thereof.

With respect to the breadth of the claims, claim 54, in part (a), is directed to polypeptides of specified amino acid sequences. Part (c) includes analogs thereof having no more than ten substitutions, deletions or additions of amino acid residues. Claims 44 and 54 have now been amended to clarify the language about the ten amino acid changes to make it absolutely clear that any such analog has no more than a total of ten amino acid residues which differ from the base sequence. Thus, part (c) now specifies that the analogs have no more than ten changes in the amino acid sequence with each such change being a substitution, deletion or insertion of a single amino acid. It further specifies that the analog must bind to MORT-1 and/or MACH. It should be noted that the amino acid sequence of SEQ ID NO:2 has 480 residues, and the amino acid sequence of SEQ ID NO:4 has 221 residues. Thus, ten changes in the 480 residue sequence amounts to only 2%, i.e., the claimed analogs have a minimum of about 98% identity to

the specified sequence. Ten out 221 is still about 95% identity for SEQ ID NO:4.

The examiner's attention is invited to the Revised Interim Written Description Guidelines Training Materials, which have been published by the Patent and Trademark Office, Example 14 "Product by Function". There, a claim to a specific sequence and variants thereof that are at least 95% identical thereto and have a specified function was held to comply with the written description requirement. The Guidelines state:

> The single species disclosed is representative of the genus because all members have at least 95% structural identity with the referenced compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

While these Training Materials relate to written description, rather than enablement, they should be instructive also from the standpoint of enablement to the extent that the Patent and Trademark Office has conceded that, with a claim such as the present, a single example is representative of the entire genus of variants with 95% identity. Thus, this is not a particularly wide breadth for an analog claim.

While claim 54 is somewhat broader than the G1 isoform of SEQ ID NOs:2 and 4, the claimed scope is necessary in order to reasonably cover the invention. In MPEP §2164.08,

relating to enablement commensurate in scope with the claims, the MPEP quotes the following from *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

It should be noted that the definitions of fragment, analog and derivative at claim 54(b), (c) and (d), respectively, all require that the fragment have the ability to bind to MORT-1 and/or MACH. Furthermore, claims 44 and 54 no longer require in the preamble that the polypeptide necessarily affects the intracellular signaling process initiated by the binding of FAS ligand to FAS-R or the binding of TNF to p55-R. The polypeptides have utility merely by binding, for example in affinity chromatography, and, therefore, it is not absolutely necessary to assay for such intracellular activity. Thus, any required testing is even simpler than before this amendment. In view of the stated activity and the direction in the specification, which will be discussed below, and the reasonable breadth of the analogs, the breadth is not unduly broad and the experimentation to find everything within the scope of these claims would not be undue.

The nature of the invention, is such that substantial experimentation is reasonably conducted by those

of ordinary skill in the art. The present claims are directed to recombinantly-produced polypeptides, DNA encoding same, and a therapeutic method. Applicants concede that there is not 100% predictability in these fields. However, this does not mean that an applicant must be limited to exemplified embodiments. As long as it is shown that the experimentation to determine what falls within the claim is not undue, the enablement requirement is met. As discussed below, the experimentation is not undue.

As to the state of the prior art, there is no close prior art. The reference cited by the examiner here is not prior art. It claims the same invention and will be the subject of an interference proceeding. Thus, there is no prior art reason for limiting the scope of the claims. Furthermore, a review of prior patents will show that it is common for those of ordinary skill in the art to take part in this degree of experimentation as there are hundreds of patents that include claims with novel proteins and analogs thereof with 95% or even less identity. This is not a case of first impression.

As to the level of one of ordinary skill, inventions involving biotechnology involve a very high level of ordinary skill. Because of this extremely high level of ordinary skill, even complex experimentation is not necessarily undue or unreasonable.

The next two *Wands* factors, the level of the predictability in the art and the amount of direction provided by the inventor, go hand in hand. As to the predictability in

the art, when changing the sequence by less than 5%, there would be an expectation that the function is maintained. Thus, it is reasonably predictable that such a small number of changes will work, but in any event, it is readily testable in order to determine which will have the claimed function and which will not have the claimed function. The present claim always requires that the result of the amino acid changes have the ability to bind to MORT-1 and/or MACH, i.e., by definition, the activity must be retained. The present specification states at page 33, lines 7-13:

> While any technique can be used to find potentially biologically active proteins which substantially correspond to G1 proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications. The proteins expressed by such clones can then be screened for their ability to bind to various MORT-1-binding proteins, such as, for example, Mch4 and MACH, or even directly to MORT-1, and/or FAS-R and p55-R mediating activity, and/or to mediating activity of any other intracellular pathway in ways noted above.

See also page 36, lines 16-19, where it states:

> When the exact effect of the substitution or deletion is to be confirmed, one skilled in the art will appreciate that the effect of the substitution(s), deletion(s), etc., will be evaluated by routine binding and cell death assays. Screening using such a standard test does not involve undue experimentation.

Furthermore, substantial guidance is provided in the present specification as to preferred substitutions which would be expected to retain the activity of the base compounds, i.e., the G1 proteins. Note, for example, page 33, line 14, through page 36, line 19. The examples in the present specification,

such as Reference Examples 1(i) and (iii), show well-known binding assays, including the two-hybrid screen and an *in vitro* binding assay using glutathione agarose beads. These are relatively simple tests. Whole libraries can be screened at one time with the yeast two-hybrid assay. Other binding assays using microarray technology are well known in the art and can test thousands of compounds at once for binding. This is not undue experimentation in this art, particularly in view of the small number of amino acids that may be changed in accordance with the language of the claims. Accordingly, it is apparent that there is substantial direction provided in the specification about how to do these standard binding assays. This is all that is necessary to do in order to determine whether any given analog having no more than ten amino acid changes has the ability to bind MORT-1 and/or MACH. These minor changes are not unreasonable. Accordingly, substantial direction is provided by the specification.

As far as working examples are concerned, as discussed above, working examples of binding assays are given in the specification and the effect of G1 proteins in these assays is provided in working examples. While there are no working examples given in the specification for analogs, fragments and derivatives, the guidance of the specification explains how to determine whether any given compound falls within the scope of the claims, and therefore additional working examples are not necessary.

Finally, the last *Wands* factor is the quantity of experimentation needed to make or use the invention based on

the content of the disclosure. It is true that substantial experimentation will be necessary. However, as stated at MPEP §2164.06, the test is not merely quantitative since a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are not the controlling factors. Procedures for making variants of the G1 protein which have at least 95% identity with the sequence thereof are conventional in the art. See page 33, lines 7-10, where the present specification states:

> While any technique can be used to find potentially biologically active proteins which substantially correspond to G1 proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications.

The assays involved to determine whether any such analog has the ability to bind MORT-1 and/or MACH are routine, as is disclosed in the specification and discussed above. All of the claimed analogs must possess the specified activity of being able to bind MORT-1 and/or MACH. There is a reduction to practice of the disclosed species of G1 proteins. The fact that any single amino acid change might have a profound effect or no effect, is not really dispositive. Here, standard binding assays are provided in the specification and so any given analog can readily be tested without undue experimentation. Indeed, whole libraries of analogs can be tested simultaneously. Thus, applicants need not rely upon predictability with analogs of respect to changes (even though

there is reasonable predictability with analogs of greater than 95% identity), but is relying on testing in the standard assays described in the specification which can be carried out in large numbers at the same time.

The level of skill in the art is high and the assays are standard and can be conducted with many different analog sequences at the same time. Thus, while substantial experimentation may be needed to establish all of the sequences of which fall within the scope of the claim, i.e., meet the functional requirement of binding to MORT-1 and/or MACH, such experimentation is not undue or unreasonable. Indeed, for any given sequence, the testing is virtually negligible in order to test for binding to MORT-1 or MACH.

The same is true with respect to fragments. Fragments can be made by removing one amino acid at a time from either end and testing for binding activity using the standard assays described in the specification and discussed above. Once the activity is lost, it would not be expected that smaller fragments would be operable. Thus, the amount of experimentation needed to find fragments is even less than that needed to find analogs.

With respect to derivatives, there is no reason to even predict that derivatizing an amino acid of a sequence will cause this sequence to lose its activity. Derivatives are defined in the present specification at page 40, lines 7-22, and are explicitly defined so as to include only those derivatives that do not change one amino acid to another of the 20 commonly-occurring natural amino acids. This is even

specified in the claims. Thus, derivatives are not analogs. They are simply standard modifications of the side groups of one or more amino acid residues, or the residues on the N- or C-terminal residues. There is no more reason that these would cause the sequence to lose its activity than for a salt. In any event, the claim requires that the activity be retained, and, if necessary, the standard binding assays discussed above can be used on the derivatives to confirm that no activity is lost. Thus, it would certainly not involve undue experimentation in order to establish that such functional derivatives have the required claimed properties.

For all of these reasons, the enablement requirement is fulfilled with respect to the full scope of claim 54. If there is enablement for the polypeptides of claim 54, there must be enablement for the DNA of claim 44 encoding same and the other claims which depend therefrom.

With respect to claims 60-62, the examiner states that the claims are not enabled for gene therapy. However, as discussed above, applicants choose not to elect gene therapy for examination in this case and have limited the method-of-use claims to protein therapy. It is believed that the examiner's rejection of the gene therapy claims is obviated by this change. This rejection would not be applicable to the protein therapy claims. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 45-52, 55-59 and 62 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that the standard claim language used by

applicants, "A molecule in accordance with claim 44," is indefinite and must state "The molecule in accordance with claim 44". Similar comments were made with respect to the vector, polypeptide and method claims. This rejection is respectfully traversed.

With respect, it is hoped that the examiner is not here trying to change over 100 years of claim-drafting practice. The language "A molecule in accordance with claim 44" is just as acceptable as the language of claim 44, which begins "A molecule ...". The "in accordance with claim 44" is merely shorthand for the rest of claim 44 being incorporated by reference. The examiner's attention is invited to MPEP §608.01(n)I.A. showing examples of acceptable dependent claim wording, all of which begin "A gadget as in ...". The examiner's attention is also invited to the fact that the dependent claims of the patent cited in the art rejection also begin with the article "An". Finally, the examiner's attention is invited to MPEP §2173.02, stating that only a reasonable degree of particularity and distinctness is necessary and some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. Applicant submits with respect that valuable examining time and valuable attorney's time should not be wasted on such minor insignificancies. Reconsideration and withdrawal of this rejection are, therefore, respectfully urged.

Claims 44(a)(b)(c), 49-53 and 54(b)(c) have been rejected under 35 U.S.C. §102(e) as being anticipated by Shu

et al. The examiner states that the DNA sequence encoding the amino acid sequence claimed by Shu is 99.8% identical to applicants' claimed DNA sequence encoding SEQ ID NO:2 and 100% identical to the applicants' claimed DNA sequence encoding SEQ ID NO:4. The examiner states that the amino acid sequence claimed by Shu is 99.8% identical to applicants' SEQ ID NO:2, and 91% identical to applicants' amino acid SEQ ID NO:4, but has 12 different amino acids and does not read on claim 44(c) or 54(c). This rejection is respectfully traversed.

First, it is not clear where in Shu there is disclosed any sequence 100% identical to present SEQ ID NO:4. The C-terminal part of SEQ ID NO:4 differs from anything disclosed by Shu. The examiner is requested to elucidate this point.

Second, as the examiner notes, Shu claims the same invention as being claimed by the present application. The present application has an official filing date of March 3, 1997, which is only slightly after the February 5, 1997, effective filing date of Shu. Because Shu claims the same invention as the present claims, applicants cannot swear back of Shu with a declaration under 37 C.F.R. §1.131. In order to antedate Shu, an interference proceeding must be initiated. Accordingly, filed on even date herewith is a Request for Interference under 37 C.F.R. §1.607, which incorporates the statement required by 37 C.F.R. §1.608(a). In view of this request for interference, the present rejection must be held in abeyance until after completion of the interference proceeding. Accordingly, reconsideration and withdrawal of

this rejection, pending institution and completion of an interference proceeding is respectfully urged.

Applicants have learned that a division of the application which issued as the Shu patent was filed on May 18, 2001, and given application no. 09/861,270. This application, which is presumably still pending, should also be considered for inclusion in any such interference.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and indication of allowability subject to the requested interference are, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Version with Markings to Show Changes Made

Claims 44, 53, 54, 57, 60 and 61 have been amended as follows:

44 (~~New~~Amended). A molecule comprising a DNA sequence encoding a polypeptide which is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH, ~~and affects the intracellular signaling process initiated by the binding of FAS ligand to FAS-R or the binding of TNF to p55-R,~~ which polypeptide has the amino acid sequence of:

(a) a G1 protein isoform whose sequence is that of SEQ ID NO:2 or 4;

(b) a fragment of (a) which is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH;

(c) an analog of (a) which differs from the sequence of (a) by no more than ten changes in the amino acid sequence of (a), each said change being a substitution~~s~~, deletion~~s~~ and/or insertion~~s~~ of a single amino acid, ~~residues and~~which analog is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH; or

(d) a derivative of (a), (b) or (c) by modification of the side groups of one or more amino acid residues thereof without changing one amino acid to another of the twenty commonly occurring natural amino acids, which derivative is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH.

53 (Amended~~New~~). A method for producing a polypeptide which is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH ~~and affects the intracellular signaling~~

~~process initiated by the binding of FAS ligand to FAS-R or the binding of TNF to p55-R~~, comprising:

growing transformed host cells in accordance with claim 52 under conditions suitable for the expression of an expression product;

effecting post-translational modifications of said expression product as necessary for obtaining said polypeptide; and

isolating said polypeptide.

54 (~~New~~Amended). A polypeptide which is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH ~~and affects the intracellular signaling process initiated by the binding of FAS ligand to FAS-R or the binding of TNF to p55-R~~, which polypeptide has the amino acid sequence of:

(a) a G1 protein isoform whose sequence is that of SEQ ID NO:2 or 4;

(b) a fragment of (a) which is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH;

(c) an analog of (a) which differs from the sequence of (a) by no more than ten changes in the amino acid sequence of (a), each said change being a substitutions, deletions and/or insertions of a single amino acid, ~~residues and~~which analog is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH; or

(d) a derivative of (a), (b) or (c) by modification of the side groups of one or more amino acid residues thereof without changing one amino acid to another of the twenty

commonly occurring natural amino acids, which derivative is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH.

57 (Amended~~New~~). A polypeptide in accordance with claim 54, ~~which has the amino acid sequence of SEQ ID NO:2 or~~wherein the sequence of (c) is an analog ~~thereof~~ which differs from ~~SEQ ID NO:2~~ the sequence of (a) by the substitution, deletion or insertion of a single amino acid residue, which analog is capable of binding to one or more of MORT-1, ~~Mch4~~ and MACH.

60 (Amended~~New~~). A method for the modulation of cell death or inflammatory processes, comprising treating said cells by introducing into said cells one or more ~~of said~~ polypeptide in accordance with claim 54 in a form for intracellular introduction thereof, ~~or introducing into said cells a DNA sequence encoding said one or more said polypeptide in the form of a vector carrying said sequence, said vector being capable of effecting the insertion of said sequence into said cells in a way that said sequence is expressed in said cells~~.

61 (Amended~~New~~). A method for the modulation of the FAS-R or TNF ligand effect on cells carrying a FAS-R or p55-R, comprising treating said cells with one or more polypeptides according to claim 54 capable of binding to MORT-1 or a MORT-1-binding protein, wherein said treating of said cells comprises introducing into said cells said one or more polypeptides in a form suitable for intracellular introduction thereof, ~~or introducing into said cells a DNA sequence encoding said one or more polypeptides in the form of a~~

~~suitable vector carrying said sequence, said vector being capable of effecting the insertion of said sequence into said cells in a way that said sequence is expressed in said cells.~~

Claim 62 has been deleted.

New claims 63-68 have been added.